Questions

nesiritide
25 May 2001

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardio-Renal Advisory Committee

Natrecor is a parenteral formulation of nesiritide (a 32-amino acid peptide, produced by recombinant DNA technology) that is identical to B-type natriuretic peptide produced by the human ventricle. Nesiritide (Natrecor) was developed for use in the in-hospital treatment of decompensated congestive heart failure (CHF).

The original NDA contained data from randomized studies enrolling 721 patients, including 505 patients who received nesiritide in a range of infusion doses between 0.003 to 0.025 microgram/kg/min. Following an Advisory Committee approval recommendation (5 for approval, 3 against approval), the Division and the Office decided not enough was known and the application was not approved. A summary of our actions at that time, including the suggestion for another trial, has been included in your background package from the Division.

In this new study (VMAC), 489 patients with exacerbations of CHF and dyspnea at rest were randomized to placebo (142), nitroglycerin (143) or nesiritide (204). The two primary endpoints (change in pulmonary capillary wedge pressure and patient self-evaluation of dyspnea) compared nesiritide to placebo at 3 hours. Patients in VMAC were followed for up to 6 months and long-term data were collected in other trials.

1. Consider pulmonary capillary wedge pressure (PCWP).
   - 1.1 Do the results of VMAC demonstrate that, compared to placebo, nesiritide decreases PCWP?
   - 1.2 Considering VMAC and earlier studies, was there a benefit on PCWP associated with the use of nesiritide when compared with ...
     - 1.2.1 ... placebo?
     - 1.2.2 ... nitroglycerin?
   - 1.3 Is demonstration that an agent decreases PCWP sufficient for its approval as a therapy for acute CHF?

2. Consider symptoms.
   - 2.1 What influence did the assessment of invasive hemodynamics in some subjects have on the evaluation of symptoms?
   - 2.2 Do the results of VMAC demonstrate that, compared to placebo, nesiritide improves symptoms?
   - 2.3 Considering VMAC and earlier studies, was there a symptom benefit associated with the use of nesiritide when compared with ...
     - 2.3.1 ... placebo?
     - 2.3.2 ... nitroglycerin?
   - 2.4 Along with hemodynamics, is demonstration that an agent reduces the symptoms of CHF sufficient for its approval as a therapy for decompensated CHF? What other clinical benefits would be acceptable alternatives?

3. Consider hypotension.
   3.1 How did the incidence, duration and severity of the hypotension associated with nesiritide compare with ...
      3.1.1 ... placebo?
      3.1.2 ... nitroglycerin?
   3.2 Were the complications associated with hypotension (e.g., increases in creatinine or acute renal failure) similar with nesiritide and nitroglycerin?
   3.3 Was the incidence of hypotension or adverse events related to hypotension on nesiritide in VMAC different from earlier studies? If so, was the difference attributable to the lower dose used in VMAC?

4. Consider morbidity.
   4.1 How important is it that a sponsor provide long-term information on morbidity (*e.g.*, hospitalization) for drugs developed as treatments of acute CHF?
   4.2 If it is important, ...
      4.2.1 ... what amount of excess morbidity should a sponsor be able to exclude?
      4.2.2 ... are the data sufficient to exclude such an adverse effect of nesiritide on morbidity?

5. Consider mortality.
   5.1 How important is it that a sponsor provide long-term mortality information for drugs developed as treatments of acute CHF?
   5.2 If it is important, ...
      5.2.1 ... what amount of excess mortality should a sponsor be able to exclude?
      5.2.2 ... are the data sufficient to exclude such an adverse effect of nesiritide on mortality?

6. Is there adequate experience on which to base a description of the safety and effectiveness of nesiritide in ...
   6.1 ... patients with CHF of acute ischemic origin?
   6.2 ... patients with CHF and preserved systolic function?
   6.3 ... patients receiving other drugs common in the treatment of decompensated CHF?

7. Is there evidence for the development of tachyphylaxis to nesiritide?

8. If nesiritide were to be approved for the treatment of decompensated CHF, what should the label say about ...
   8.1 ... the patient population?
   8.2 ... the benefits of treatment?
   8.3 ... dose?
   8.4 ... duration of treatment?
   8.5 ... effects on symptoms?
   8.6 ... effects on mortality?
   8.7 ... the need for central monitoring?
   8.8 ... any special warnings or contraindications?

9. Should nesiritide be approved for the treatment of decompensated CHF?